REMARKS/ARGUMENTS

Amendments to the Claims

New claims 15-35 directed to various embodiments of the invention are added in order to better specify and distinguish the claimed invention.

Specific kidney disfunctions and nephropathies are now stated in the new claims and the wording directed to a subject at risk to be affected by the disfunction or nephropathy renders the scope of the term "prevention" clearer. No new subject-matter has been added.

Response to Double Patenting Rejection

Claims 9-14 are rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. 6,653,349. A Terminal Disclaimer is submitted herewith in order to overcome the double patenting rejection.

Claim Rejections – 35 USC §112, first paragraph

The specification provides enablement for "preventing a kidney dysfunction" for the following reasons:

Nature of the invention: the claims are drawn to a method for reducing the probability of all forms of nephropathy due to nephrotoxic drugs or environmental contaminants. The nature of the invention is well defined and it is not complex. Nephropathies due to nephrotoxic drugs and environmental contaminants are well known in the art; *see* Galley, H.F., J. R. Coll. Surg. Edinb., 45, February 2000, 44-50[1], a copy of which is attached.

Breath of Claims: claims are drawn to a method for reducing the probability of all forms of nephropathy due to nephrotoxic agents, drugs (lithium, antibodies, anticancer drugs) or environmental contaminants (mycotoxin).

Nephrotoxic agents are well known: diuretics, ß-blockers, systemic vasodilators such as sodium nitroprusside or angiotensin converting enzyme ACE inhibitor, NSAIDs anti-inflammatory drugs, cyclosporin antibiotics such as aminoglycosides and vancomycin, lactams, rifampicin, sulphonamides, vancomycin and ciprofloxacin, anti-fungal agents such as amphotericin, cytotoxic agents such as cisplatin, radiocontrast media, heavy metals, organic

[1] This article has been listed on a PTO/SB/08A form and the examiner is requested to acknowledge receipt and review of this documentation so it will be part of the official record of this file.

solvents such as carbon tetrachloride, plant and animal toxins, mannitol, protease inhibitor indinavir, chemotherapic agents, ethylene glycol (antifreeze); *see* Galley, *supra*.

Guidance in the Specification: the specification gives *in vivo* experimental working examples that support the present invention. More in particular, the protective activity against (experimentally induced) renal insufficiency "crush syndrome" was tested by administering acetyl L-carnitine and propionyl L- carnitine three days preceding the test (see pages 4 and 5), showing the preventive effect of the invention; the test shows, in addition, comparative data of the composition vs. acetyl L-carnitine or propionyl L-carnitine alone.

Protection against the mycotoxin produced by *Aspergillus ochraceus* is shown in the working examples on pages 6-7.

Protection against lithium is shown in the assay on page 7-9.

State of the Art: US patent 5,246,835 to Suzuki et al refers to the clinical diagnosis of diabetic nephropathy characterised by continuous proteinuria. The diabetic patients with proteinuria develop into terminal renal insufficiency within 5 or 6 years. The reference explains that it is difficult to cure nephropathy, and specific indication is to diabetic nephropathy, nothing is the about difficulty of preventing nephropathy due to nephrotoxic agents. The skilled person is aware that proteinuria is not a nephrotoxic agent and will know that it is different from tubular-interstitial nephropathy and tubular necrosis due to toxic agents (see pages 6 to 9).

Predictability of the Art: The specification gives significant guidance to the prevention method of the present invention since, as previously mentioned, experimental results support the claims. Moreover, experimental results are based on state of the art, peer-recognized experimental models on laboratory animals. *See* literature references in the working examples.

The working examples show the protective effect of the combination of the invention against some toxic agents.

The skilled person is aware that these results are predictable of the same protective effect in the case of prevention. Namely, the protective effect will occur also when the subject takes the combination of the invention before coming into contact with the toxic agent. Obviously, the skilled person -- in this case it can be the same subject to be treated -- knows that the method for prevention is carried out when the subject is at risk of being contaminated.

For example, the experiment on ochratoxin A provided in the description provides an embodiment of the invention applicable in those circumstances in which a subject, or a skilled person taking care of that subject, knows the patient to be at risk of coming into contact with contaminated food.

Mutatis mutandis the same reasoning applies to the example dealing with lithium contamination.

Starting from the working examples, the skilled person is able to carry out the invention throughout the whole range of the claims. Namely, the skilled person, having the knowledge of nephrotoxic agents, is able to carry out the invention with those subjects who are likely to come into contact with these agents (for example workers in risky environments), or must come into contact with these agents (for example patients affected by a certain disease who must take drugs which are nephrotoxic).

The Amount of Experimentation Necessary: the specification gives experimentation in an appropriate and acknowledged in the scientific community animal model system to determine that the claimed combination is effective in preventing kidney dysfunctions.

In view of the results, fully explained in pages 4-9, the skilled person would have enough guidance to repeat the process successfully without undue experimentation.

In view of the above applicant submits that claims 9-35 are enabled by the instant specification.

Response to Claim Rejection – 35 USC §103

Claims 9-14 stand rejected as being "obvious" over a single reference. US Patent 5,955,424 to Calvani et al teaches a therapeutic method for inhibiting nephrotoxicity and vasculotoxicity induced by administration of Cyclosporin A, by orally or parenterally administering to a patient in need thereof a composition comprising an effective amount of both of Cyclosporin A and an alkanoyl L-carnitine wherein, the alkanoyl L-carnitine is preferably propionyl L-carnitine. Nephrotoxicity induced by cyclosporin A is a result of a general arterial disease which is associated with tubular atrophy and glomerular ischemia. Cyclosporin A is a vasculotoxic immunosuppressive drug (column 1 lines 16-25 and 64-65).

Calvani teaches that an alkanoyl L-carnitine, preferably propionyl L-carnitine, acts on the vascular system.

In the present case the combination of acetyl L-carnitine and propionyl L-carnitine is used to prevent the onset of kidney dysfunctions that can be induced by several nephrotoxic agents (see the previous list) which can act on the kidney physiology and functionality.

No indication is given by Calvani et al on the capability of the combination of acetyl L-carnitine and propionyl L-carnitine of protecting the kidney from several toxic agents. No other effect other than the effect on the vascular system is disclosed in Calvani et al.

One of ordinary in the art, with the problem of preventing nephrotoxic effects from toxic agents, these agents acting directly on kidney functionality, would not be motivated by Calvani et al to combine propionyl L-carnitine with acetyl L-carnitine in order to prevent kidney damage. In fact, Calvani et al's teaching is limited to the vasculotoxic effect of Cyclosporin A. The skilled person learns from Calvani et al that the vasculotoxic effect is the primary consequence of Cyclosporin A and the secondary effect is a nephropathy induced by ischemic effect deriving from arterial (vasculotoxic) disease. In fact, Calvani et al act on the arterial district in order to indirectly treat kidney disfunction. To the contrary, the present invention acts directly on the kidney (*see* pages 7-9, experiment on isolated kidney).

Calvani et al limit their teaching to the combination of <u>one</u> alkanoyl L-carnitine, preferably propionyl L-carnitine, with Cyclosporin A. There is no teaching in Calvani et al to combine <u>two specific</u> alkanoyl L-carnitines, namely acetyl and propionyl. Calvani et al teach at least 6 different alkanoyl L-carnitines, i.e. acetyl, propionyl, isopropionyl, butyryl, isobutyryl, ter-butyryl. The 15 possible combinations of coupling two specific alkanoyl L-carnitines would compel the skilled person to an undue burden of experimentation.

In order to render obvious a claim, the state of the art must provide all the elements constructing it. In the present case a number of elements of the claimed invention are lacking from the cited reference.

- Inhibiting vs preventing: Calvani et al achieve a different technical effect than the present invention. Calvani achieves the inhibition, i.e. the non occurrence of an effect (nephrotoxic effect of an immunosuppressant agent). The present invention achieves the prevention of a harmful effect. This means that the effect could occur, but the level of harm is not so dangerous as it would be without the protective effect. *See*, for example, Table 2 in the

specification: the abnormality levels are the closest to the normal levels when the present invention is carried out.

- The presence of the toxic agent: Calvani et al teach the reader to administer one single member of the carnitine family with the toxic agent. The present invention teaches to administer a combination of two specific members of the carnitine family before the possible contact with the toxic agent.

- The selection of specific members of the carnitine family: while Calvani et al induce the skilled person to think that each member of the carnitine family is equivalent, the present invention selects only two specific members. There is no indication in the prior art to select these two and only two members.

- The differences: at least three main differences occur between the present invention and the prior art: a) the effect achieved by the prior art and the present invention, b) the manner of carrying out the prior art and the invention, and c) the technical means to carry out the prior art the present invention.

✓ a) the skilled person, with the problem of preventing kidney disfunction or nephropathy from the contact with toxic agents, will look for solutions to the problem in the prior art. Calvani et al teach the clinician to inhibit the effect of an immunosuppressive agent by co-administering the agent together with one of any of the members of carnitine family. Following this teaching, the skilled person will not arrive at the present invention, where the prevention is achieved by administering the protective combination of the invention *before* the subject comes into contact with the toxic agent (*see* description, page 8, third full paragraph);

✓ b) referring to the previous point, Calvani et al do not suggest the possible administration of a combination of carnitines before the possible occurrence of the contact with the toxic agent;

✓ c) Calvani et al do not suggest one to select two specific members of the carnitine family, to combine them and to administer them before the occurrence of the contact with the toxic agent. Moreover, and most important, Calvani et al, as explained above, teach how to inhibit indirect toxic effect on kidney of a substance, due to arterial disease brought about by the toxic agent. The skilled person knows that, in order to ascertain the toxic effect, specific parameters are to be measured. *See* the description: enzymuria in Table 2 and

histamine in Table 3. Calvani et al do not teach one to look at these parameters. Hence, the skilled person does not know if the carnitines will have any effect on the parameters to be measured. Therefore, the skilled person, having the full family of carnitines provided by Calvani, would not be able to select the two specific members of the present invention, to combine and administer them before occurrence of the contact with the toxic agent and to check specific parameters in order to assess the effect brought about by the combination.

The prior art provides none of the elements necessary in order to find out and combine the technical features to arrive at the claimed subject matter.

For the above reasons it is respectfully submitted that claims 9-35 define enabled, patentable subject matter. Reconsideration and allowance are solicited. Should the examiner require more information, please contact the undersigned.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Arthur R. Crawford
Reg. No. 25,327

ARC:eaw
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100